REMARKS

Priority

The specification has been amended to replace two separate priority statements with one combined priority statement as suggested by the Examiner.

Enablement Rejection

Claims 1-5 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 1 has been amended to recite a method of stimulating osteoblast differentiation and bone formation *in vitro*. The method involves the step of over-expressing Smad1 in osteoblast precursor cells, wherein the Smad1 interacts with Hoxc-8 protein and inhibits the binding of the Hoxc-8 protein to a BMP-responsive gene encoding a bone matrix protein. This method of inducing osteoblast differentiation and bone formation has been described in detail and is fully supported by disclosure in Example 18 and Figure 7. As determined by the standard bone formation marker alkaline phosphatase, Example 18 clearly illustrates

induction of osteoblast differentiation by over-expressing Smad1 in osteoblast precursor cells. Claim 4 further limits the BMP-responsive gene to osteopontin, which is described in Example 12 as containing Hoxc-8 binding element.

Consequently, Applicant submits that the specification has provided sufficient disclosure commensurate to the scope of the claimed method, and no undue experimentation is required to practice the claimed method of stimulating bone formation. Accordingly, Applicant respectfully requests that the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph, be withdrawn.

Written Description Rejection

Claims 1-5 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with written description requirement. The rejection is respectfully traversed.

As discussed above, claim 1 has been amended to recite a method of stimulating osteoblast differentiation and bone formation *in vitro* by over-expressing Smad1 in osteoblast precursor cells. In view of the disclosure of Example 18, Applicant submits that the specification has conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in

possession of the claimed invention. Accordingly, Applicant respectfully requests that the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejections Under 35 USC §112, 2nd Paragraph

Claims 1-5 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

The Examiner contends that the term "Smad1" renders the claims vague and indefinite. Claim 1 has been amended to recite a method of using Smad1 which mediates signaling of bone morphogenetic protein, a member of the TGF-β superfamily. Applicant submits that signal transduction in the TGF-β superfamily and proteins that mediate the signaling such as Smad1 are intensively studied and well-known in the art. It is well characterized that signal transduction in the TGF-β superfamily is mediated by direct phosphorylation of Smad proteins including Smad1 (page 17, line 11 to page 18, line 1). Hence, in the area of TGF-β superfamily signal transduction, one of ordinary skill in the art could readily recognize and distinguish the structure and function of Smad1.

Applicant hereby lists a number of scientific papers as evidences that at the time the instant application was filed, the state of the art was that TGF-β superfamily signal transduction was intensively studied and signaling proteins such as Smad1 was well-known in the art: (1) Naco et al., (1998) Expression of Smad1 and Smad2 during embryogenesis suggests a role in organ development. *Dev. Dyn.* 211:293-305; (2) Kretzschmar and Massague, (1998) SMADs: mediators and regulators of TGF-beta signaling. *Curr. Opin. Genet. Dev.* 8:103-111; (3) Kretzschmar et al., (1997) Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1. *Nature* 389:618-622; (4) Kretzschmar et al., (1997) The TGF-beta family mediator Smad1 is phosphorylated directly and activated functionally by the BMP receptor kinase. *Genes Dev.* 11:984-995; (5) Lagna et al., (1996) Partnership between DPC4 and SMAD proteins in TGF-b signaling pathways. *Nature* 383:832-836; (6) Macias-Silva et al., (1998) Specific activation of Smad1 signaling pathways by the BMP7 type I receptor, ALK2. *J. Biol. Chem.* 273:25628-25636.

In view of the above description of the state of the art, Applicant submits that one of ordinary skill in the art would readily

recognize the metes and bounds of the protein encompassed by the term "Smad1" with regard to signal transduction in the TGF-β superfamily. Accordingly, Applicant respectfully requests that the rejection of claims 1-5 under 35 U.S.C. §112, second paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed October 22, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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